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Islet Cell Transplantation for the Treatment of Non-uremic Type 1 Diabetic Patients with Severe Hypoglycemia

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This Health Technology Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the report are welcome and should be sent to:

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SUMMARY

- Type 1 diabetes, a chronic metabolic disorder characterized by the presence of hyperglycemia, is primarily caused by a progressive destruction of insulin-producing beta cells in the pancreatic islets. Type 1 diabetes accounts for 10% of all cases of diabetes and is accompanied by long-term complications such as heart disease, stroke, blindness, kidney disease, and nervous system damage.
- The current standard of care for type 1 diabetes includes insulin therapy, dietary restrictions, and physical activities. Hypoglycemia is the most common complication of intensive insulin therapy, preventing patients from achieving optimal glucose control. According to the Canadian Diabetes Association Clinical Practice Guidelines, insulin therapy characterized by increased frequency of glucose monitoring, increase in the glucose targets, and multiple insulin injections with increased glucose targets was recommended to be used for individuals with hypoglycemia unawareness.
- Beta cell replacement either by whole pancreas transplantation or by islet cell transplantation may be an alternative to intensive insulin therapy for patients with type 1 diabetes. The majority of pancreas or islet cell transplants were performed in combination with kidney transplantation for type 1 diabetic patients with end-stage renal disease because of the need for immunosuppression. Pancreas transplantation alone or islet cell transplantation alone was also suggested for non-uremic type 1 diabetic patients with severe hypoglycaemia.
- This report focuses on the use of islet cell transplantation alone (ITA) for a subgroup of type 1 diabetic patients who have severe hypoglycemia and uncontrolled diabetes but without kidney disease. Evidence on the efficacy/effectiveness of ITA for this group of patients is limited. To date, no randomised controlled trials were conducted to compare the efficacy of ITA to other treatments such as intensive insulin therapy or whole pancreas transplantation in controlling hyper- and hypoglycemia.
- The Edmonton protocol for ITA addresses several drawbacks of previously used approaches. It consists of a steroid-free immunosuppressive regimen, isolation and purification of islets in xenoproteins-free medium, short cold ischemic time, and transplantation of adequate number of viable islet cells.

- The results from the Edmonton series on ITA for non-uremic type 1 diabetic patients look promising. As of January 2002, 17 patients received the Edmonton protocol. Of 15 consecutive patients with at least 1-year follow-up after the initial transplant, 12 patients were insulin independent at 1-year post transplant. No episode of hypoglycemia was observed after transplantation. Results from two very small clinical studies regarding the efficacy of ITA in restoring hormonal responses to hypoglycemia are inconclusive.
- ITA appears to be a safe procedure. The risks involved in ITA primarily relate to the procedure itself and the immunosuppressive regimens. None of the serious surgical complications that may occur with whole pancreas transplantation were evident.
- Limited evidence suggests that ITA is effective in controlling labile diabetes and protects against unrecognised hypoglycemia in highly selected patients in the short term. The long-term effects of ITA on metabolic control remain to be proven. Follow-up studies are needed to determine the duration of this metabolic effect in order to assess its potential for preventing or arresting the development of chronic diabetes complications in non-uremic type 1 diabetic patients with severe hypoglycemia. Future research is required to improve measures for islet mass/function in order to appropriately evaluate the effects of the ITA procedure.
- The Immune Tolerance Network launched and implemented a 2-year international multi-centre trial at ten islet transplantation centres to confirm and extend the results from the Edmonton team. The trial, funded jointly by the National Institute of Health and Juvenile Diabetes Foundation, will replicate the Edmonton protocol in a total of 40 patients.
- Based on the limited published evidence, islet cell transplantation in non-uremic type 1 diabetic patients with severe hypoglycemia or uncontrolled diabetes is an evolving procedure with promising results but it is not yet considered a 'standard of care' for this group of patients.
- The Alberta Health Ministry recognizes the potential benefits of ITA for type 1 diabetic patients who have severe hypoglycemia or uncontrolled diabetes despite compliance with an insulin regimen and is currently providing special public funding for Alberta residents who meet the program's criteria.

GLOSSARY

Autonomic – self-controlling; functionally independent [1].

Autonomic nervous system – the portion of the nervous system concerned with regulation of the activity of cardiac muscle, smooth muscle, and glands [1].

Basal C-peptide – is a protein that is attached to insulin produced in the body. When insulin is secreted by the pancreas, C-peptide is released in the blood stream. The C-peptide blood levels can indicate whether or not a person is producing his/her own insulin [2].

Cold ischemic time – the time measured from the point at which blood flow to the organ is stopped in the donor to the time that the blood flow to the organ is restored to the recipient [3].

Creatinine – is a protein produced by muscle and released into the blood. The amount produced is relatively stable in an individual. The creatinine level in the serum is therefore determined by the rate it is being removed, which is roughly a measure of kidney function. If kidney function falls, the creatinine level will rise [4].

End-stage renal disease – also known as chronic kidney failure. A condition in which patients need dialysis treatment or a transplant to perform the lost functioning of the kidney [3].

Euglycemia – blood glucose level within the normal range [1].

HbA_{1c} – glycosylated hemoglobin, provides a measurement of one's average blood sugar level [2].

Hyperglycemia – abnormally increased concentration of glucose in the blood [1].

Hypoglycemia – abnormally diminished concentration of glucose in the blood [1].

Mild hypoglycemia – an episode in which a patient feels symptoms related to activation of adrenergic (tachycardia, palpitations, shakiness) or cholinergic (sweating) defense mechanisms or the effects of hypoglycemia on the nervous system (reduced ability to concentration, dizziness, hunger, blurred vision) but is not sufficiently impaired to interfere with normal activities or to seek treatment [5].

Moderate hypoglycemia – an episode in which a person's neurological status is marked by obvious impairment of motor function, confusion, or inappropriate behaviour but still alert enough to seek self-treatment [5].

Panel reactive antibody (PRA) – the percentage of cells from a panel of donors with which a potential recipient's blood serum reacts. The more antibodies in the recipients blood, the more likely the recipient will react against the potential donor. The higher the PRA, the less chance of receiving an organ that will not be rejected [3].

Severe hypoglycemia – an episode of hypoglycemia resulting in coma, seizure, or sufficient neurological impairment so that the patient is unable to initiate self-treatment and requires the assistance of another person [5].

Hypoglycemia unawareness – a condition in which moderate to severe hypoglycemia occurs without any warning symptoms. This is largely an iatrogenic syndrome in which recurrent, often silent, hypoglycemia reduces both the awareness of and defense mechanisms against subsequent hypoglycemia [5].

Insulin – a protein hormone secreted by the beta cells of the pancreatic islets in response to elevated blood levels of glucose and amino acids and promotes the efficient storage and utilization of these fuel molecules [1].

Liver function test – a blood test that measures the levels of liver enzymes in the blood as a way of helping diagnose liver problems [6].

Non-uremic – without kidney disease.

Pancreatic islets – irregular microscopic structures scattered throughout the pancreas and comprising its endocrine portion. In humans, they are composed of at least four types of cells: the *alpha cells*, which secrete the hyperglycemic factor glucagon; the *beta cells*, which are the most abundant and secrete insulin; the *delta cells*, which secrete somatostatin; and the *PP (or F) cells*, which secrete pancreatic polypepetide [1].

ABBREVIATIONS

IAK – islet transplantation after kidney transplantation

IE – islet equivalents

ITA – islet transplantation alone

ITN – Immune Tolerance Network

min – minute

mo – month

PAK – pancreas transplantation after kidney transplantation

PRA – panel reactive antibody

PTA – pancreas transplantation alone

RCT – randomized controlled trial

SIK – simultaneous islet and kidney transplantation

SPK – simultaneous pancreas and kidney transplantation

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Tables and Figures:

INTRODUCTION

This report was prepared in response to a request from Alberta Health and Wellness (AHW) for information about the use of islet cell transplantation for patients with type 1 diabetes. AHW was specifically interested in the current status of islet cell transplantation using the Edmonton protocol for a sub-population of non-uremic patients with type 1 diabetes who have severe hypoglycemia or uncontrolled diabetes despite compliance with an insulin regimen. The question of interest was whether this procedure could be deemed to be a standard of medical care for this group of patients.

Clinical background

Diabetes mellitus is a chronic metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action, or both [7]. Type 1 diabetes, formerly known as insulin-dependent diabetes mellitus, is primarily caused by a progressive destruction of insulin-producing beta cells in the pancreatic islets [8]. Beta-cell destruction can be autoimmune mediated or caused by unknown mechanisms [9].

The clinical symptoms of type 1 diabetes are usually not detected until after the patient's own immune system has covertly attacked and destroyed 90% or more of the total beta-cells of the endocrine pancreas [7]. Type 1 diabetes is accompanied by long-term complications such as heart disease, stroke, hypertension, blindness, kidney disease, nervous system damage, and amputations that are the causes of most of the morbidity and mortality [10].

Epidemiology

Diabetes is a serious health problem. Diabetes is the seventh leading cause of death in Canada [11]. Over two and a quarter million Canadians are estimated to have diabetes, and 10% of these cases are of type 1 [11]. It is estimated that there are currently more than a million patients with type 1 diabetes in the United States, and 30,000 new cases identified annually [12].

Diabetes is a major cause of coronary artery disease, the leading cause of death in Canada. Diabetes is also a leading cause of new cases of blindness and kidney disease in adults [9].

Treatment options

Avoidance of the acute and long-term complications is a major concern in the management of diabetes [9]. In addition, the person's quality of life and overall sense of well-being are an integral part of management [9]. The current standard of type 1 diabetes care includes multiple, daily subcutaneous insulin injections, frequent glucose

monitoring, dietary restrictions, physical activity, and close attention to factors such as illness and stress levels [2,12].

Insulin therapy

According to the Canadian Diabetes Association, glucose control will depend on the coordination of insulin doses, food intake, and physical activity for people with type 1 diabetes [9]. Most people with type 1 diabetes should aim for optimal glucose levels to prevent or delay microvascular complications of diabetes [9]. To achieve target glucose levels multiple daily injections (three to four per day) or the use of continuous subcutaneous insulin infusion as part of an intensified diabetes management regimen are usually required [9].

Hypoglycemia is the most common complication of insulin therapy in patients with type 1 diabetes [5]. Intensive insulin therapy does not achieve normal levels of blood glucose [13] and frequently causes hypoglycemia, which can lead to coma and possibly death. It is estimated that 4% of deaths in patients with type 1 diabetes are the result of hypoglycemia [13]. The Diabetes Control and Complications Trial (DCCT) of the National Institute of Diabetes and Digestive and Kidney Diseases found that a total of 65% of patients in the intensive treatment group versus 35% of patients in the conventional treatment group had at least one episode of severe hypoglycemia at an average follow-up of 6.5 years [14]. Data from DCCT indicated that, while hyperglycemia is associated with progressive complications, intensive insulin therapy has been associated with a three-fold increased risk of hypoglycemia [10]. The findings from a meta-analysis [15] demonstrate that the risk of severe hypoglycemia is increased by intensive insulin therapy and that this increase depends on the degree of blood glucose normalization achieved.

The major risk factors for severe hypoglycemia include a prior episode of severe hypoglycemia, a current low HbA_{1c} (less than 6%), hypoglycemia unawareness, long duration of diabetes and autonomic neuropathy [16]. Usually patients with long-standing type 1 diabetes have severely impaired alpha cell function resulting in impaired hypoglycemia-induced hormonal counterregulation [17]. The normal acute defense mechanisms against insulin-induced hypoglycemia consist primarily of glucagon release from the alpha cells of the pancreatic islet followed shortly thereafter by epinephrine release from the adrenal medulla [18]. In the early stages of diabetes mellitus, patients retain the ability to release glucagon and epinephrine during hypoglycemia. However, within several years the glucagon response begins to diminish and is then lost in most patients [18]. Eventually, the epinephrine response is also compromised although usually not totally absent [18].

Normally when blood glucose is abruptly lowered by insulin injections, diabetic patients will experience symptoms beginning with feeling of warmth, hunger, and sweating and, in severe cases, visual blurring, confusion, and even death [18].

Hypoglycemia unawareness occurs when patients with recurrent hypoglycemia gradually lose their ability to sense low circulating glucose levels so they may develop severe hypoglycemia without any milder warning symptoms [18].

Severe hypoglycemic reactions are the main barrier to achieving optimal glucose control in people with type 1 diabetes [16, 19]. The insulin-based management of hyperglycemia for diabetes must choose less meticulous maintenance of glycemia and HbA_{1c} levels as a method of diminishing symptom recognition [18]. According to the Canadian Diabetes Association clinical practice guidelines, for individuals with hypoglycemia unawareness, the strategies include increased frequency of glucose monitoring, increase in the glucose targets, and multiple insulin injections with increased glucose targets [16]. Several groups [19-21] found that careful loosening of insulin-based management and avoidance of hypoglycemia result in the return of early symptom awareness to diabetic patients which thereby place the patient at less risk for serious hypoglycemic episodes. However, this loosening of glycemic control by exogenous insulin usually leads to higher degrees of glycemia in the patient, which increases the risk for complications of chronic hyperglycemia [18].

Beta cell replacement

Replacing islet cells either by whole pancreas transplantation or by transplantation of islet cells may be an alternative to insulin injection for patients with severe hypoglycemia and hypoglycemia unawareness. Transplanted islets which contain all types of endocrine cells may provide benefits in several ways: 1) functioning beta cells lead to better control of blood glucose changes; 2) functioning alpha cells may release glucagon when blood glucose decreases, especially in those patients who still need some exogenous insulin after islet transplantation [22].

Since the first successful simultaneous pancreas and kidney transplantation in 1966 [23], more than 16,000 pancreas transplantations have been performed worldwide [24]. Because of the need for immunosuppression, the majority of pancreas transplantation procedures were performed either simultaneously (SPK) or subsequent to (PAK) kidney transplantation for type 1 diabetic patients with end-stage renal disease. About 5% of the total transplants were pancreas transplantations alone (PTA) performed in patients with hypoglycemia or unstable diabetes without long-term diabetic complication to improve glycemic control and quality of life [24-26].

At present pancreas transplantation is the only treatment for type 1 diabetes that consistently establishes both euglycemia and insulin independence [13]. The 1997-2001 data from the International Pancreas Transplantation Registry [24] indicated that the 1-year rate of graft survival (defined as total freedom from insulin therapy, normal fasting blood glucose concentrations, and normal or only slightly elevated HbA_{1c} values) was 83% for SPK, 79% for PAK, and 78% for PTA for cadaveric pancreas transplants performed in the United States. The mortality rate at one and three years

after pancreas transplantation is approximately 7% whether SPA, PAK, or PTA is used [18].

Patients who are severely metabolically unstable, have severe autonomic dysfunction, or generally have a very poor quality of life because of the effects of chronic diabetes are candidates for PTA [23]. Graft survival rate is lower for PTA. This may partly be related to the fact that detection of pancreas rejection is easier when the procedure is SPK or PAK [18]. Clinical research demonstrated that successful pancreas transplantation improves epinephrine response and normalizes hypoglycemia symptom recognition in patients with long-standing diabetes and established autonomic neuropathy [18]. However, the correction in glucagons and epinephrine responses is probably not complete after pancreas transplantation [27]. In addition, some investigators found that symptomatic or asymptomatic hypoglycemia occurred in patients who received successful pancreas and kidney transplantation [26]. The primary aetiology of post pancreas transplantation-associated hypoglycemia remains unknown [26].

According to the American Diabetes Association [28], pancreas transplantation should be considered an acceptable therapeutic alternative to continued insulin therapy in diabetic patients with imminent or established end-stage renal disease who have had or plan to have a kidney transplant. In the absence of indications for kidney transplantation, pancreas transplantation should only be considered a therapy in patients who exhibit these three criteria: 1) a history of frequent, acute, and severe metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) requiring medical attention; 2) clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; 3) consistent failure of insulin-based management to prevent acute complications [28].

Pancreas transplantations are major surgical interventions associated with some significant risks from the procedure itself. Those who receive pancreas transplantation require life-long immunosuppression that may be associated with high morbidity and significant mortality rates [29].

Compared to whole pancreas transplantation, islet cell transplantation offers the advantage of being able to be performed as a minimally invasive procedure [30].

OBJECTIVE AND SCOPE

The objectives of this report were to systematically review the medical literature on the efficacy/effectiveness and safety of islet cell transplantation for non-uremic type 1 diabetic patients who have severe hypoglycemia or uncontrolled diabetes despite compliance with an insulin regimen and to provide scientifically sound rational for determining the status of this procedure for this specific sub-group of patients (see Methodology in Appendix A). The use of islet cell transplantation combined with kidney transplantation for type 1 diabetic patients with end-stage renal disease is not addressed in this report.

DESCRIPTION OF ISLET CELL TRANSPLANTATION

Overview

Investigation of pancreatic islet cell transplantation as a potential procedure to reverse diabetes has been ongoing since the early 1970s [31]. Islet cell transplantation procedure involves procurement of donor pancreases, islet isolation from a donor pancreas and purification, infusion of islets percutaneously into the liver via the portal vein, and application of life-long immunosuppressive regimen while the islet cells are functioning [2].

Islet cell transplantation can be either an autotransplantation (transplantation within the same individual) or an allotransplantation (transplantation from a donor). In this report, the term islet cell transplantation refers only to islet allotransplantation. There are four different recipient categories for islet cell transplantation [32]:

1. islet after kidney or simultaneous islet and kidney transplantation for type 1 diabetic patients who are already immunosuppressed with a kidney allograft or are about to receive one;
2. islet transplantation alone (ITA) for non-uremic type 1 patients with hypoglycemic unawareness;
3. islet transplantation for totally pancreatectomized patients receiving a simultaneous orthotopic liver transplant because of upper gastrointestinal malignancy or liver failure; and
4. islet transplantation for patients with type 2 insulin-requiring-diabetes undergoing orthotopic liver transplantation.

Islet cell transplantation has been mostly performed in combination with kidney transplantation for type 1 diabetic patients with end-stage renal failure [33]. These patients require an immunosuppression regimen to prevent the rejection of the transplanted kidney and therefore the islet graft would not present an additional risk [33].

According to the International Islet Transplant Registry, a total of 445 adult islet allotransplantations for patients with type 1 diabetes have been performed worldwide (mostly in North America and Europe) from 1974 through December 2000 [34]. The majority of these transplantations were performed since 1990 [34]. Before 1999 the results of human islet cell transplantation have been disappointing compared to whole pancreas transplantation. Of the 267 islet transplantations performed from 1990 to 1999, insulin independence after one year was achieved in only 8% of the patients [35]. Some of the factors that may be contributing to poor long-term function of the islets include difficulties associated with the islet isolation technique, inadequate number of

transplanted islets, and the diabetogenic effects of the conventional immunosuppressive therapy [13, 36].

The Edmonton protocol

In July 2000, Shapiro and his colleagues published results of successful islet transplantation in seven non-uremic type 1 diabetic patients who had recurrent severe hypoglycemia or metabolic instability and did not respond to treatment with exogenous insulin [37]. All seven patients achieved insulin independence at one year after transplantation. The protocol adopted by the Edmonton team incorporated several new approaches to islet transplantation, and is known as the Edmonton protocol.

Novel immunosuppressive regimens

Immunosuppression has been based on triple therapy with azathioprine, prednisolone, and cyclosporine A (CsA) for the last two decades [32]. It is now recognised that CsA impairs islet replication, islet engraftment and beta cell function. Both CsA and tacrolimus treatment are associated with nephrotoxicity. Tacrolimus is also more neurotoxic and more diabetogenic compared to CsA. The combination of steroids and high dose tacrolimus and CsA induced a marked insulin resistance and direct beta cell toxicity [33].

The Edmonton group used a steroid-free immunosuppressive regimen comprised of a combination of sirolimus, low dose tacrolimus and daclizumab. This immunosuppressive regimen is less likely to cause diabetes after transplantation and is also less harmful to the kidney.

Preparation of islet cells

In the past, xenoprotein products, such as fetal calf serum, were used in many islet transplantation centres to isolate and purify donor islet cells [38]. Islets were often transplanted after several days in culture [39].

In the Edmonton series, donor islet cells were isolated and purified in xenoprotein-free medium to avoid targeting by formed antibodies that facilitate cell destruction by complement activation or antibody-dependent cellular cytotoxicity. Cold ischemic time was kept short and islet cells were transplanted less than 12 hours after harvesting them [40].

Delivery of an adequate number of viable islet cells

In the past, the threshold of 360,000 islets (6,000 IE/kg), which represents the approximate number of islets currently isolated from a pancreas, was considered necessary for graft function [41].

In the Edmonton series, more islets (approximated 11,000 IE/kg) were extracted from at least two pancreas donors and were given to recipients several weeks apart. The

number of islets used by the Edmonton team was therefore almost double that previously used.

Selection of patients with life-threatening hypoglycemia and brittle diabetes

Islet transplantation was mostly prescribed for type 1 diabetes patients who had a functioning kidney transplant and were already using immunosuppressive drugs. Islet cell transplantation in this group of patients was only rarely successful, partly because the usual immunosuppressive drugs used in kidney transplantation caused diabetes and harmed the transplanted islets.

Patients selected in the Edmonton clinical series were without end-stage renal disease, thus had no previous transplantations of kidney or other solid organs. Selection of recipients was based on recurrent severe hypoglycemia or metabolic instability with no response to treatment with exogenous insulin.

Efficacy of ITA for Non-uremic Type 1 Diabetic Patients

No randomised controlled or other controlled clinical trials have been conducted to compare the efficacy of ITA with that of either insulin therapy or whole pancreas transplantation for non-uremic type 1 diabetic patients with severe hypoglycemia or uncontrolled diabetes. All studies on islet cell transplantation for this group of patients are case series or small clinical studies.

A number of case series studies that reported the use of islet cell transplantation combined with kidney transplantation for type 1 diabetic patients with end-stage renal failure were excluded from this review because the patient populations involved in these studies are different from the patient group of interest (see Appendix B for excluded studies).

Three islet transplantation centres in Canada [17, 40], Germany [42], and the United States [43] have published their experiences with ITA for non-uremic type 1 diabetic patients with hypoglycemia unawareness or severe diabetic complications. In July 2000 Shapiro and colleagues reported the results of ITA using the Edmonton protocol in seven non-uremic type 1 diabetes patients who had a history of severe hypoglycemia or uncontrolled diabetes despite compliance with an insulin regimen [37]. All seven patients were reported to have quickly attained sustained insulin independence after transplantation (median follow-up of 11.9 months, range from 4.4 to 14.9 months).

Since the first publication of their success [37], several articles have been published to update the data on the previous cases and to report their results on new cases [40, 44-46]. Only the study with the most recent results [40] is assessed and presented in this report. Two clinical studies [17, 42] with very small sample sizes investigated the effects of ITA on restoring hypoglycemia-induced hormonal counterregulation. Details of these studies are summarised in Table 1.

Table 1: Efficacy of ITA for non-uremic type 1 diabetic patients

Study/study objective	Patient	Intervention	Outcome	Conclusion
Ryan et al. 2002 [40] Canada **Objective**: to report longer-term outcomes of islet transplantation and delineate issues related to the procedure.	**N** = 17 **Condition:** type 1 non-uremic diabetic patients with severe hypoglycemia **Duration of diabetes:** Mean 27.2±2.8 years **Age:** mean 39.7±2.0 years **N** = 10 volunteers (6 women, 4 men; age 32±4years) were studies as control subjects for metabolic tests.	**Procedure:** ITA **Number of donor pancreas used:** 2-4 **Number of islets transplanted:** mean 12,330±581 IE/kg **Immunosuppression:** Sirolimus Tacrolimus Daclizumab **Follow-up:** Median 20.4 months (range 3.2 to 34.2 months) from the first transplant	**Insulin independence** 80% insulin independence at 1 year after the first transplantation. 4 out of 6 patients were insulin independent after 2 years post-transplantation **Glycosylated hemoglobin (HbA_{1c})** 8.48±0.49 (pre-transplant) versus 5.8±0.13 (most recent value post-transplant) ($p<0.001$) in 11 patients who were off insulin. **C-peptide** C-peptide response improved after transplantation and stimulated C-peptide values were equivalent to those of control subjects. Of the 11 patients off insulin, 8 had a detectable C-peptide secretion. Fasting C-peptide was maintained over prolonged follow-up. **Hypoglycemia** All the patients off insulin had stable glucose values and did not have hypoglycemic reactions.	Prolonged insulin independence can be achieved after islet transplantation. There are acute risks related to the procedure and risks associated with the immunosuppressive drugs. The insulin reserve is not normal but adequate to correct the problems of glycemia. Careful patient selection remains essential to maximize the risk-benefit ratio for any individual patient.

Table 1: Efficacy of ITA for non-uremic type 1 diabetic patients (cont'd)

Study/study objective	Patient	Intervention	Outcome	Conclusion
Goss et al. 2002 [43] USA **Objective:** to report transplantation experience with type 1 diabetes mellitus patients using pancreatic islets processed at an established remote pancreatic islet isolation center.	**N** = 3 **Condition:** type 1 non-uremic diabetic patients with severe hypoglycemia and metabolic instability. C-peptide not detected in any of the patients before transplantation. **Duration of diabetes:** at least 5 years **Age:** 36-47 years	**Procedure:** ITA **Number of donor pancreas used:** 1-2 **Number of islets transplanted:** Patient 1: 13,375 IEQ/kg Patients 2: 19,703 IEQ/kg Patient 3: 10,240 IEQ/kg **Immunosuppression:** Sirolimus Tacrolimus Daclizumab **Follow-up:** Patient 1: 4 months Patient 2: 3 months Patient 3: 0.5 month	**Insulin independence** All 3 patients attained sustained Insulin independence after first transplantation. **Glycosylated hemoglobin (HbA_{1c})** Patient 1: 8.7% (pre-transplant) versus 5.7% (4 months post-transplant) Patient 2: 9.1% (pre-transplant) versus 5.9% (3 months post-transplant) Patient 3: data not available **C-peptide** Serum C-peptide was not detectable in any of the three patients (<0.05 ng/mL) before transplantation. All 3 patients consistently had a fasting C-peptide level > 1.5 ng/mL (normal 0.09-1.9ng/mL) after islet transplantation. **Hypoglycemia** None of the patients had an episode of hypoglycemia after islet transplantation.	These data demonstrated that insulin independence can be achieved by pancreatic islet transplantation using pancreatic islets isolated at a remote processing center and pancreatic islet isolation techniques and experience can be concentrated at a small number of regional facilities.

Table 1: Efficacy of ITA for non-uremic type 1 diabetic patients (cont'd)

Study/study objective	Patient	Intervention	Outcome	Conclusion
Meyer et al. 1998[42] Germany **Objective:** to test the hypothesis that successful Intraportal islet transplantation could improve hormonal glucose counterregulation and hypoglycemia awareness in patients with long-standing type 1 diabetes.	**N** = 3 **Condition:** type 1 non-uremic diabetic patients with severe hypoglycemia, **Duration of diabetes:** 20-34 years **Age:** 31-39 years **N** = 10 normal controls (matched by age and body mass index)	**Procedure:** ITA **Number of donor pancreas used:** 1 **Number of islets transplanted:** Patient 1: 440,000 IE Patient 2: 964,000 IE Patient 3: 565,000 IE **Immunosuppression:** Methypredinisolone Cyclosporine Monoclonal anti-CD4 mice antibody All immunosuppressive drugs were withdrawn 4 weeks after transplantation. **Follow-up:** approximately two months	**Insulin independence** Insulin independence was achieved in one patient over 14 days and insulin requirement reduced in the other two patients after transplantation. Islet transplants were rejected 2 months after withdrawal from immunosuppressive therapy in all patients. **Glycosylated hemoglobin (HbA_{1c})** No significant change in glycosylated hemoglobin levels occurred after transplantation. **C-peptide** C-peptide secretion was absent in all 3 patients before transplantation. Two to 3 weeks after transplantation basal plasma C-peptide level averaged 0.27, 0.65, and 0.41 nmol/L in 3 patients, respectively. Basal C-peptide levels <0.16 nmol/L approximately 2 months after withdrawal from immuno-suppressive therapy in all patients. **Hypoglycemia** No severe hypoglycemia occurred within 2 months after transplantation. **Hormonal responses** No improvement in the glucagons response one month after successful transplantation; Glycemic thresholds and/or peak incremental responses of epinephrine, norepinephrine, and cortisol improved in all patients after transplantation; All patients developed autonomic warning symptoms.	Intraportal islet transplantation does not restore hypoglycemia-induced glucagons secretion, but it improves the responses of most counterregulatory hormones, including epinephrine, and regenerates hypoglycemic warning symptoms even in patients with long-standing type 1 diabetes. Intraportal islet transplantation should be an alternative treatment in carefully selected patients with type 1 diabetes, in whom recurrent episodes of severe hypoglycemia occur despite intensive patient education, frequent self-monitoring of blood glucose levels, and safe treatment goals.

Table 1: Efficacy of ITA for non-uremic type 1 diabetic patients (cont'd)

Study/study objective	Patient	Intervention	Outcome	Conclusion
Paty et al. 2002 [17] Canada **Objective:** to determine whether glucagons and epinephrine responses and hypoglycemic symptom recognition are improved after successful islet transplantation.	**N** = 7 (first 7 recipients in the Edmonton series as reported in Shapiro et al. [37]) **Condition:** type 1 diabetes with hypoglycemia unawareness and severe metabolic instability **Duration of diabetes:** mean 27±6 years **Age**: 30-54 (mean 43±3 years) **N** = 7 controls with type 1 diabetes (matched by age and weight) **N** = 7 normal controls (matched by age and weight)	**Procedure:** ITA ***Number of donor pancreas:** 2-4 ***Number of islets transfused:** 11,547±1,604 IE/kg ***Immunosuppression:** Sirolimus Tacrolimus Daclizumab **Follow-up:** Mean duration of insulin independence for all patients was 12.6±0.6 months from the time of the final islet infusion. * Information from Shapiro et al. [37]	**Insulin independence** Insulin independence was achieved in all 7 patients. Mean duration of insulin independence was 12.6±0.6 months from the time of the final islet infusion. **Glycosylated hemoglobin (HbA_{1c})** Data on HbA_{1c} not available. No significant differences in the mean fasting and sequential 45-min glucose levels among the three groups. **C-peptide** No statistical differences in the plasma C-peptide levels between the islet transplant recipients and control subjects during the clamp. **Hypoglycemia** None of islet transplant recipients recognized any symptoms of hypoglycemia until a plasma glucose level ≤50mg/dl. **Hormonal responses** No significant rise in the mean plasma glucagons level in transplanted group during the clamp. The mean incremental glucagon response (basal to 180 min) of the transplanted group was significantly less than that of normal control group ($p<0.05$), and was not significantly different from that of the type 1 diabetic group. Overall no significant rise in plasma epinephrine. The mean incremental epinephrine response (basal to 180 min) of transplanted group was significantly less that that seen in the control group ($p<0.05$), and was not significantly different from that of patients with long-standing type 1 diabetes.	The results indicate that despite providing prolonged insulin independence and near-normal glycemic control in the patients with long-standing type 1 diabetes, hypoglycemic hormonal counterregulation and symptom recognition were not restored by intra-hepatic islet transplantation.

According to the most recent published results of the Edmonton series, as of January 1, 2002, 54 islet transplantation procedures were performed on 30 patients and 17 of these patients completed the Edmonton protocol [40] (see Figure 1). The median follow-up time for these 17 patients was 20.4 months with a range of 3.2 to 34.2 months from the first transplant. Of 15 consecutive patients with at least 1-year follow-up after the initial transplant, 12 patients (80%) were insulin independent. As of January 1, 2002, out of the 17 patients, 11 remained insulin free. The follow up data on six patients who are now more than two years post-transplant indicates that four of these patients remain off insulin. According to the authors, the results suggest that long-term insulin independence can be achieved.

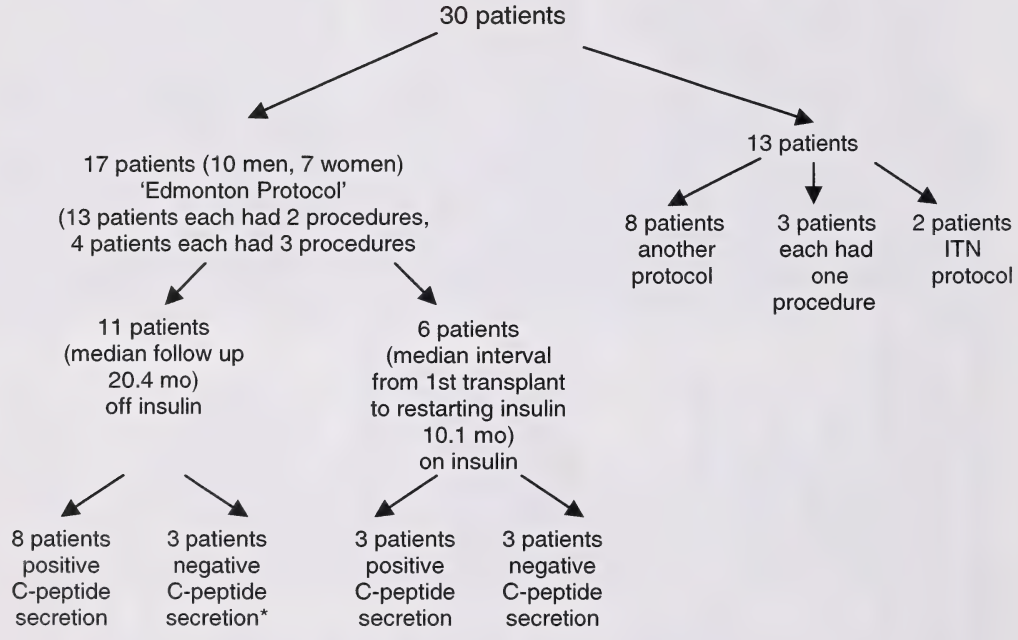

Figure 1: Follow-up of Edmonton case series [40]

* Note: patients can be considered insulin independent but have severely impaired islet function.

In the 17 patients at median follow-up of 20.4 months from initial transplant, HbA_{1c} levels decreased from pre-transplant values of 8.21±0.36% to the most recent values of 6.08±0.77% ($p<0.001$) (a normal value for HbA_{1c} is <6.1%) Of the 11 patients who were still off insulin as of January 1, 2002, HbA_{1c} levels decreased from pre-transplant 8.48±0.49% to the most recent values of 5.8±0.13% ($p<0.001$) at a median follow up of

20.4 months. These 11 patients have diabetes according to the American Diabetes Association criteria and two of them were on oral hypoglycemic agents because of increased glucose levels. In eight of these 11 patients there were detectable levels of C-peptide secretions. Of the six patients who were back on insulin, three C-peptide positive patients required a much lower daily insulin dose than their pre-transplant use of insulin. Daily insulin doses required for the other three C-peptide negative patients were not reported. Pre- and post transplant HbA_{1c} levels were not reported for these six patients who were back on insulin treatment. All the patients off insulin had stable glucose values and did not have hypoglycemic episodes.

Diabetes complications observed in the 17 patients included progression of retinopathy (three patients required laser photocoagulation), rise in blood pressure post-transplant (10 patients), and rise of cholesterol (15 patients, in four patients cholesterol levels dropped again with diet therapy). No significant changes were observed in renal function or neuropathy.

According to Shapiro, 49 Canadian patients have now received islet cell transplantations at the University of Alberta, and the 1 year insulin independence rate for completed transplants was 84% (Shapiro, personal communication, Jan 2003). The details of these 49 cases were not yet published. The Edmonton protocol, which has undergone a number of recent modifications (2-layer pancreas preservation, changes in islet culture, and use of other non-steroidal immunosuppressant strategies), has been replicated in over 15 islet transplant centres involving over 160 patients worldwide [47]. However, these results have not yet been published.

Goss and colleagues [43] recently reported their experience with islet cell transplantation in three non-uremic type 1 diabetic patients using pancreatic islets processed at an established remote pancreatic islet isolation centre. Pancreatic islets were isolated using xenoprotein-free media. Immunosuppressive regimen consisted of sirolimus, tarcrolimus, and daclizumab, as in the Edmonton protocol. Two patients received two procedures and the other one received one procedure. More than 10,000 IE/kg were given to the each patient. Post-transplant follow-up for these three patients was at 4, 3, and 0.5 months, respectively. All three patients achieved insulin independence after their first pancreatic islet transplantation. The mean glycosylated hemoglobin values were reduced after transplantation. Serum C-peptide was not detectable in any of the patients before transplantation. After transplantation all three patients had consistently a fasting C-peptide level within the normal range. None of the three patients had an episode of hypoglycemia after transplantation.

Two studies [17, 42] specifically looked at the effects of ITA on restoring hypoglycemia-induced hormonal counterregulation and on hypoglycemia awareness in type 1 diabetic patients. Meyer and colleagues [42] investigated the secretory response of counterregulatory hormones and hypoglycemia awareness before and after successful

ITA in three patients with long-standing type 1 diabetes. Ten non-diabetic control subjects were matched for age and body mass with islet transplant recipients. All three patients received islets from single donor pancreas. Immunosuppressive drugs were withdrawn four weeks after islet transplantation to minimize their confounding effect. Insulin independence was achieved in one patient over 14 days and the two other patients required significantly less daily insulin after ITA. Islet transplants were rejected in all subjects approximately two months after withdrawal from the immunosuppressive therapy. There were no significant changes in glycosylated hemoglobin levels after islet transplantation. All three type 1 diabetic patients had multiple episodes of severe hypoglycemia in the previous year but none of them experienced such hypoglycemia at approximately two months after transplantation. This study found that while ITA does not restore hypoglycemia-induced glucagons secretion, it improves the responses of most counterregulatory hormones and hypoglycemic warning symptoms even in patients with long-standing type 1 diabetes.

Paty and colleagues [17] compared hormone responses and hypoglycemic symptom recognition in seven insulin independent patients who received ITA using the Edmonton protocol, to seven non-transplanted type 1 diabetic patients and to seven non-diabetic controls, who were matched for age and weight with the islet transplant patients. The study showed that glucagons and epinephrine responses and hypoglycemic symptom recognition were not improved by islet transplantation. This result is partially contrary to the findings reported by Meyer and colleagues [42].

SAFETY OF ISLET CELL TRANSPLANTATION

A recent publication on the Edmonton case series [40] reported details on the complications associated with islet transplantation, which included procedure-related complications and immunosuppressive regimen-related complications. Other studies [42,43] also reported complications observed after islet transplantation, although the follow-up periods in these studies were quite short. All complications reported in these studies are summarized in Table 2.

Procedure-related complications

Based on the data from 54 islet transplantation procedures performed in 30 patients, Ryan and colleagues [40] noted a number of procedure-related complications, including transient bradycardia, moderate bleeding at the site of the transhepatic puncture, thrombosis of a peripheral branch of the right portal vein, moderate abdominal pain, and puncture of the gallbladder. In 46% of cases, liver function test results rose to more than twice normal levels and returned to normal within a median time of 22 days post-transplant. Acute bleeding from the liver surface was resolved by reduction in the dose of heparin and the use of hematostatic Gelfoam. The peripheral portal vein thrombosis was resolved by the use of anticoagulative treatment.

The study by Goss and colleagues [43] did not find any complications related to the islet transplantation procedure. The other study [42] did not report any procedure-related complications.

Immunosuppressive regimen-related complications

Based on the observations of 17 patients who received the Edmonton protocol with a median follow-up of 20.4 months, the most serious adverse event was a significant increase in serum creatinine. Other complications included increased urine proteins, mild and superficial mouth ulcers, acne, arthralgias, rheumatoid arthritis, diarrhea, anaemia and decreases white blood counts.

In the Edmonton trial, the complications caused by immunosuppressive treatments were resolved by lowering the dose or changing the form of the relevant drugs. No patients developed cytomegalovirus infection or disease, post-transplant lymphoproliferative disorders, malignancies, or serious infections. None of the serious surgical complications that may occur with whole-pancreas transplant were evident in any of these patients, and the islet transplantation procedure was simple and very well tolerated.

Goss and colleagues [43] did not find any complications related to the immunosuppressive regimen, although the follow-up was short.

Casey and colleagues [48] recently reported the results of portal venous pressure changes after islet cell transplantation using the Edmonton protocol in 50 consecutive transplantation procedures in 26 patients. Highly purified islets (mean purity 72%), mixed with 35 U/kg of heparin, were injected into the main portal vein. Of the 26 patients, 8 (31%) had a single islet infusion, 12 (46%) had two procedures, and 6 (23%) had three procedures. The analysis showed that the acute post-transplant mean portal pressure rose significantly between the first, second, and third transplants ($p<0.001$). The mean acute change in portal pressure from baseline during the islet infusion also increased significantly with the number of islet transplants performed ($p<0.001$). However, the increase in portal pressure was transient. No patient showed clinical evidence of portal hypertension. Liver function tests in these patients were normal at a median follow-up of 16.9 months, but the long-term consequences of these acute changes remain unknown.

Table 2: Complications of islet cell transplantation

Study	Procedure-related complications	Immunosuppression-related complications
Ryan et al. 2002 [40] Follow-up: median 20.4 months (3.2 to 34.2) in 17 patients who completed the Edmonton protocol.	Transient bradycardia (2 patients), Moderate bleeding at the site of the transhepatic puncture (5 patients, 4 required blood transfusion and one of them required transfusion and surgery), Thrombosis of a peripheral branch of the right portal vein (2 patients), Moderate abdominal pain (12 patients), Puncture of the gallbladder (2 patients), Abnormal liver function test: in 46% of cases, liver function test results rose to more than twice normal levels and returned to normal within a median time of 22 days post-transplant.	Significant increase in serum creatinine (2 patients who had elevated creatinine levels pre-transplant), Increase in urine protein (4 patients), Mild and superficial mouth ulcers (15 patients), Acne (2 patients), Arthralgias (1 patient), Rheumatoid arthritis (1 patient), Diarrhea (10 patients), Anaemia (8 patients), Decrease in white blood counts (number of patients was not stated).
Goss et al. 2002 [43] Follow-up: 4, 3, and 0.5 months in 3 patients, respectively.	No procedure-related complications occurred.	No immunosuppression-related complications occurred.
Meyer et al. [42] Follow-up: approximately 2 months in 3 patients.	Data not available	Data not available

Summary of Other HTA Reports

Two technology assessment reports on pancreatic islet transplantation for patients with type 1 diabetes mellitus prepared by the Institute for Clinical Systems Improvement (ICSI) [49] and ECRI [50] were located. These two reports were not considered to be systematic reviews.

According to ICSI [49], pancreatic islet transplantation appears to be safe with low mortality and acceptably low morbidity. Although the number of patients treated was small, the efficacy of islet transplantation with respect to insulin independence, glycemic control, and serum C-peptide levels has improved dramatically in the past two years at certain islet transplantation centers. The improvement noted was attributed to changes in procedures for processing the islet cells, the number of islets transplanted, and the immunosuppressive regimens. The population of patients most appropriate for transplantation, however, remains to be determined. The report suggests that, at present, due to difficulties with harvesting adequate numbers of islet cells and the need for evidence of the reproducibility (effectiveness) of the procedure, islet transplantation is not a viable treatment option for most patients with type 1 diabetes mellitus.

According to the ECRI report [50] no published guidelines or standards were identified on islet cell transplantation alone. ECRI concluded that islet cell transplantation rarely (10%) resulted in insulin independence for any length of time, and it was rarer still for graft function to be maintained for two years or longer. Partial function of transplanted islets appeared to be useful for reducing the amount of insulin needed daily, for better maintenance of euglycemia, and for preventing hypoglycemic episode. The latter function may be mediated by a mechanism independent of glucagon release and was the chief rational for islet cell transplantation alone in patients who have hypoglycemia insensitivity of life-threatening hypoglycemic episodes. As the ECRI report was published in 2000 it did not include the results from the Edmonton case series.

Current Opinion on the Status of Islet Cell Transplantation

According to an expert from the International Islet Transplant Registry, in Europe, as well as in the United States, islet cell transplantation is still considered research, as opposed to solid organ pancreas transplantation, which is considered to be established clinical practice [51]. In Germany, islet transplantation alone is not yet seen as a "standard of medical care" among the diabetologists and endocrinologists. It is considered as a therapy with very high potential for non-uremic diabetic patients with hypoglycemia unawareness or uncontrolled diabetes despite compliance with an insulin regimen (Brendel, personal communication, Oct 2002).

In Germany, islet cell transplantation received funding support for several years as a therapeutic model. The funding was halted in 1999 (Brendel, personal communication, Nov 2002). Islet cell transplantation is not covered by Medicare in the United States [50].

A guideline on pancreas transplantation produced by the American Diabetes Association [28] states: "pancreatic islet cell transplants hold significant potential advantages over whole-gland transplants. Islet cell transplantation is an experimental procedure, also requiring systemic immunosuppression, and should be performed only within the setting of controlled research studies".

According to the Canadian Diabetes Association clinical practice guidelines, insulin therapy characterized by increased frequency of glucose monitoring, increase in the glucose targets, and multiple insulin injections with increased glucose targets was recommended to be used for individuals with hypoglycemia unawareness [16]. Neither pancreas transplantation nor islet cell transplantation were mentioned in these guidelines as treatment options for this group of patients. Experts at the Canadian Diabetes Association were contacted but failed to provide any comments on the roles of pancreas transplantation or islet cell transplantation in the management of type 1 diabetes with severe hypoglycemia and hypoglycemia unawareness. At present, intensive insulin therapy with special caution should be considered the standard of care for this group of patients. The problem with this strategy is that glycemic control will be compromised to reduce the risk of hypoglycemia and thus increase the possibility of long-term diabetic complications.

The Alberta Health Ministry, recognizing the potential benefits of ITA, is currently providing special public funding for Alberta residents who meet the program's criteria. ITA for patients with type 1 diabetes who have severe hypoglycemia despite compliance with an insulin regimen is not an insured service yet. The procedure is also available to qualified candidates from other provincial/territorial jurisdictions on a full cost recovery basis (Skinner, Feb 2003, letter to other provinces/territories).

Ongoing International Multi-centre Clinical Trials

The Immune Tolerance Network (ITN) launched and implemented a 2-year international multi-centre trial at ten centres (seven North-American and three European clinical islet transplant centres) to confirm and extend the results from the Edmonton team. The trial, funded jointly by the National Institutes of Health and the Juvenile Diabetes Foundation, will replicate the Edmonton protocol in a total of 40 patients (four patients per centre) [52].

For this trial, major efforts are underway to standardize procedures of islet isolation and transplantation, and to implement cell processing standards in accordance with good clinical manufacturing practice [53]. Each clinical site has identical equipment; personnel extensively trained in the methods of the Edmonton protocol; drugs and reagents from the same manufacturing lots to ensure consistency; and strict guidelines necessitating that the clinical site must be 'certified' prior to conducting its first transplant.

In December 2001, the first of the 40 patients in the ITN trial was transplanted in Edmonton, Canada [53]. Preliminary data indicates that the Edmonton protocol has been successfully replicated across the nine centres involved in the ITN trial, with patients now rendered independent of insulin immediately after the transplants, and 20% of these patients achieved insulin independence with a single-donor islet transplant (Shapiro, personal communication, Jan 2003).

By 2003 it is anticipated that all 40 patients will have received islet transplantation using the Edmonton protocol and data from this multi-centre trial will help to answer the questions of reproducibility and longevity of success [54].

DISCUSSION

Issues related to the Edmonton protocol

Based on the limited evidence from several clinical studies, ITA appears to be safe and effective in controlling labile diabetes and protecting against unrecognised hypoglycemia in highly selected type 1 diabetic patients. The Edmonton protocol, based on the steroid-free immunosuppressive protocol, has been used in 49 non-uremic type 1 diabetic patients and 84% of these patients achieved insulin independence at 1-year of follow up (Shapiro, personal communication, Jan 2003). No episode of hypoglycemia occurred after islet transplantation in any of these studies [40, 42, 43], although the follow-up for most studies (except for the Edmonton series) was short. Several modifications to the conventional ITA approaches, including the steroid-free immunosuppressive regimen, islet preparation in xenoproteins-free media, and transplantation of fresh islets from multiple donors, are associated with this success.

While the effects of ITA on pancreatic beta cell function (secretion of insulin) as shown in the studies by the Edmonton research team and other islet transplantation centres look promising, the effects of ITA on pancreatic alpha cell function (secretion of counterregulatory hormones such as glucagon and epinephrine) in long-standing type 1 diabetes remain unresolved. The Canadian study [17] involving seven patients in the Edmonton series suggests that ITA did not restore hypoglycemic hormonal counterregulation or symptom recognition after insulin independence.

The German study [42] involving three patients used before and after transplantation comparisons and found that ITA did not restore hypoglycemia-induced glucagon secretion, but it improved the responses of most counterregulatory hormones and hypoglycemic warning systems. This study differed substantially from the Canadian study [17]. First, the transplantation protocols including immunosuppressive regimens used in the two studies were different. Secondly, the immunosuppressive regimen was discontinued in the German study [42]. Thirdly, hormonal counterregulatory responses were measured at the different points of time in the two studies (that is, two months after islet transplantation in the German Study [42] versus more than one year after the transplantation in the Canadian study [17]). Clearly, more studies need to be done in this area.

The Edmonton protocol has been evolving to accommodate clinical problems encountered. For example, the dose of tacrolimus was lowered after kidney damage occurred in two recipients, and the dose of heparin was increased after portal venous thrombosis occurred in two patients [40]. Other recent modifications include transplantation from a single donor, 2-layer pancreas preservation, changes in islet culture, the use of other non-steroidal immunosuppressant strategies, and

preconditioning patients' immune systems with Campath [47, 55]. The advantages and disadvantages of each approach needs to be explored. For example, compared to single donor transplantation, transplantation from multiple donors can provide sufficient islet cells but may cause transient increase in portal venous pressure [48] or portal hypertension. Patients who receive transplantation from multiple donors also have an added potential risk of developing a high level of antibodies, which makes it more difficult to match cells or organs from donors in the future [55]. In 49 consecutive islet cell transplants performed in the Edmonton trial, only one patient had a temporary rise in panel reactive antibody (PRA), and the PRA level returned to normal (Shapiro, personal communication, Feb 2003).

The most important barriers to more widespread islet transplantation using the Edmonton protocol are the availability of sufficient donor organs and the uncertainty of long-term steroid-free immunosuppressive therapy [56-58]. According to the experts in the field [8, 59, 60], the future challenges include:

- need for more trials of islet transplantation,
- advances in single donor protocols,
- development of tolerance protocol to reduce therapeutic risk,
- developments in alternative insulin-producing sources,
- improvements in measures of islet mass/function to appropriately evaluate the efficacy/effectiveness of islet transplantation,
- development of effective markers of islet rejection to allow the possibility of reversing episodes of rejection before critical function losses, and
- understanding of the beneficial effects of islet transplantation on long-term secondary complications of diabetes.

Issues related to determining status of ITA

As mentioned earlier, the evidence on the efficacy/safety of ITA for non- type 1 diabetic patients mainly comes from small case series or small clinical studies with repeated measurements. No data from controlled clinical trials were available at this time. Thus, evidence that can provide strong support of the use of ITA for a subgroup of type 1 patients is currently lacking.

A modified Delphi study conducted by the Alberta Heritage Foundation for Medical Research resulted in the development of a preliminary set of criteria based on the level of available evidence for determining the status of a technology [61]. A consensus by a very select group of Alberta decision makers indicated that the status of a health technology would be considered to fall in the range of experimental to not yet

adequately validated, when no controlled studies were reported but several published case series were indicating positive results on a cumulative total of more than 20 cases and when these findings were supported by expert opinion. Some other important aspects that were identified by the Delphi study need to be taken into account when making funding decisions. In order of priority these included: levels of benefit compared to alternative intervention, quality of life or functional status, survival advantage, regulatory status in Canada or the USA, overall cost to the health care system, severity of condition, and availability of expertise [61]. Among these elements, quality of life was identified as an important factor. In regards to this aspect, a pilot study was carried out to assess the feasibility of measuring health-related quality of life in patients with type 1 diabetes (Johnson, conference abstract, Oct 2-5, 2002) but no firm conclusion can be drawn at this time.

Hypoglycemia is caused by exogenous insulin injection. Theoretically, once the need for exogenous insulin therapy is abolished by a successful islet transplant, hypoglycemia and hypoglycemia unawareness would be no longer a concern (Sutherland, personal communication, March 2003). From this perspective, islet transplantation (either whole pancreas alone or islet cell transplantation alone) would be an attractive alternative to intensive exogenous insulin treatment for patients with hypoglycemia (Sutherland, personal communication, March 2003). Several aspects need to be taken into consideration in this regard. First, evidence indicates that hypoglycemia still occurred even after successful pancreas transplantation [26]. On the other hand, the Edmonton series found that 11 patients who were off insulin after islet cell transplantation did not have any hypoglycemia episodes at median follow-up of 20.4 months. This result needs to be extended and confirmed by other islet transplantation centres. Secondly, it is difficult to determine whether the potential benefits in terms of prevention of severe hypoglycemia outweigh the risks of life-long immunosuppressive treatments in patients who do not need concomitant kidney transplantation [27]. Thirdly, most studies on counterregulation and hypoglycemia unawareness following pancreas transplantation have been done in patients with kidney transplantation [27], the true effects of pancreas transplantation alone for non-uremic patients need further investigation. In the case of islet cell transplantation alone, the results in the reduction of hypoglycemia episodes look promising. Data on the long-term outcome of reduction in secondary complications due to diabetes are not yet available.

CONCLUSION

Evidence on the use of ITA for non-uremic type 1 diabetic patients is limited as it is based on studies with weak methodological design. To date, no randomized controlled or large controlled clinical trials were conducted or proposed to compare islet cell transplantation to other treatments such as intensive insulin therapy or whole pancreas transplantation. Assessment of efficacy and safety of ITA are based on several small case series studies or small clinical studies. The results from these studies are mixed since the objectives of their research and the protocols for the transplantation procedures were different at each centre although the patients seemed to be clinically similar.

The Edmonton protocol consisting of a steroid-free immunosuppressive regimen seems promising and is considered to be a major breakthrough since the results from the first seven patients were published in 2000. The protocol itself continues to evolve. Of 15 consecutive patients who received islet cell transplantation using the Edmonton protocol, 12 patients were insulin independent at 1 year post transplant. No episode of hypoglycemia was observed after transplantation. The results regarding the effect of ITA on restoring hormonal responses to hypoglycemia are inconclusive at this time.

The risks involved primarily relate to the procedure itself and the immunosuppressive drugs. However, none of the serious surgical complications that may occur with whole pancreas transplantation were evident.

Limited evidence from the Edmonton series suggests that ITA is effective in controlling labile diabetes and protects against unrecognized hypoglycemia in highly selected patients in the short term. The long-term effects of islet transplantation on metabolic control remain to be proven. As noted by the Edmonton researchers, it is essential that the risk-to-benefit ratio be in favour of the islet transplant when considering islet transplantation. The risk associated with islet transplantation must be less than the risks of no transplantation in these patients. Thus, patients with very brittle diabetes or a severe reduction of hypoglycaemic awareness have been selected as suitable candidates. As well, a risk/benefit assessment in this group of patients must be individualized. An elevation of creatinine appears to be a contraindication for this immunosuppressive regimen. The overall long term effects of the immunosuppressive regimen remain unknown. There seems to be uncertainty about when to take patients off the immunosuppression therapy, particularly for those patients who are insulin independent but with negative C-peptide secretion.

Follow-up studies are needed to determine the duration of this metabolic effect in order to assess its potential for preventing or arresting the development of chronic diabetes complications in non-uremic type 1 diabetes patients with severe hypoglycemia. Future

research is required to determine which monitoring tests correlate to glycemic control, as a patient can be considered insulin independent but has severely impaired islet function as indicated by their C-peptide secretion. Improved measures of islet mass/function are needed to appropriately evaluate the effectiveness of the procedure.

Based on the limited research published to date, islet transplantation in non-uremic type 1 diabetic patients with hypoglycemia unawareness or uncontrolled diabetes is an evolving procedure with promising results but is not yet considered a 'standard of medical care'.

The Immune Tolerance Network has initiated an international multi-centre clinical trial to replicate the Edmonton protocol. Data from this trial will help to determine the reproducibility of the benefits of ITA reported to date.

APPENDICES

APPENDIX A: METHODOLOGY

Search strategy

A comprehensive literature search of the electronic databases was conducted using the terms listed in the table below. The first search was completed in August 2002 and the search was updated in December 2002. With the exception of the Cochrane Library and Internet searches, the literature searches were restricted to the period 1992 to December 2002. Additional searches of PubMed were conducted periodically throughout the project. Researchers in the field were also contacted for information on studies in progress.

Database Searched	Subject Headings (bolded) AND Textwords
PubMed (searched December 11, 2002)	1. see related articles to PMID 12086945 OR (islets of langerhans transplantation AND (diabetes mellitus OR diabetes) OR "islet cell transplant*" OR islets transplant*" 2. Supplementary references: islets of langerhans transplantation NOT (diabetes mellitus OR diabetes) Limit: human studies, 1992-2002
EMBASE (Ovid) (1988-2002 Week 49)	exp pancreas islet transplantation/ OR "islet cell transplants$".mp. AND exp diabetes mellitus/ Limit: human studies, 1992-2002
CINAHL (Ovid) (1982-October, Week 4, 2002)	Exp islets of langerhans/ AND (exp transplantation/ OR "transplantation".mp. Limit: 1992-2002
The Cochrane Library (2002, issue 4)	Islets of langerhans AND transplantation OR "islet transplant*"
Web of Science (Social Sciences Citation Index and Science Citation Index only) (Searched December 11, 2002)	(Islet* AND transplant* AND diabetes) NOT (rat OR mice OR dog*) Limit: 1992-2002
Bioethicsline (1973-December 2000)	Islet cell transplant$.mp. OR islets of langerhans transplantation
CRD databases (HTA, DARE, NHS EED) (Searched December 11, 2002)	Islet (automatically truncates to include islets) Diabetes AND transplantation
Biological Abstracts (SilverPlatter) (1991-June 2002)	(islets of langerhans transplantation OR islet cell transplantation) AND diabetes AND humans
Ovid HealthSTAR (1975-October 2002)	Exp islets of langerhans transplantation Limit: human, 1992-2002, non-MEDLINE

Additional Internet sites checked:

- ClinicalTrials.gov
- National Research Register
- HTA agency web sites per the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) checklist (www.ccohta.ca)

Selection of studies

Two researchers (Bing Guo and Paula Corabian) reviewed the abstracts and determined the inclusion or exclusion of the article based on the following criteria. To be included the study had to meet the following criteria:

- The study focused on pancreatic islet cell transplantation or pancreatic islet cell allotransplantation.
- Participants were patients who had type 1 diabetes for more than 5 years, with a history of severe hypoglycemia or hypoglycemia unawareness, but without severe impairment in kidney function. No restriction on age and gender.
- Study designs included randomised controlled trial, controlled clinical trial, cohort study, case control study, and case series.
- English journals from 1992 to 2002.

Studies which meet one of the following criteria were excluded:

- Procedure included islet cell auto-transplantation, xeno-transplantation (or xenogeneic transplantation), fetal pancreatic islet transplantation, liver-islet transplantation, kidney-islet transplantation, lung-islet transplantation, pancreas transplantation, and liver transplantation.
- Studies only focused on technical aspects of islet cell isolation, purification, and storage.
- Studies focused on immunosuppressive drug treatment only.
- Participants were patients with type 2 diabetes or type 1 diabetes with severe nephropathy, post-transplant diabetes, chronic pancreatitis, pancreas tumour, and previous other organ transplantation (kidney or lung).
- Abstracts, comments, letters, and notes.
- Animal studies.

If it was not certain whether an article should be included or excluded, the full text of the article was retrieved.

Data extraction

Two researchers (Bing Guo and Christa Harstall) reviewed the primary studies and independently extracted data from the primary studies. Information extracted from the primary studies included:

- Authors, year, and country of the studies.
- Patients:
  - Number,
  - Condition,
  - Age.
- Intervention:
  - Type of islet transplantation,
  - Number of donor pancreas used,
  - Number of islet cells transplanted,
  - Duration of follow-up,
  - Immunosuppressive regimen.
- Outcome measured:
  - Insulin independence,
  - Glycemic control,
  - C-peptide level,
  - Episode of hypoglycemia,
  - Hypoglycemic hormonal counterregulation.
- Complications:
  - Procedure-related complications,
  - Immunosuppression-related complications.

Assessment of methodological quality

Since all studies included in this report are small case series or small clinical studies, no formal criteria were used to assess the methodological quality of included studies.

Selection of external reviewers

External reviewers with clinical expertise in islet cell transplantation and health technology assessment methodologies evaluated the draft review and provided feedback. In selecting reviewers, the practice of AHFMR is to choose experts who are well recognized and published in the peer reviewed literature, and who can offer a provincial and/or national perspective with respect to the use or practice of islet cell transplantation.

Appendix B: Excluded Studies

The following studies focused on the islet cell transplantation combined with kidney transplantation for type 1 diabetic patients with end-stage renal failure and thus were not included in the report.

- Alejandro R, Burke G, Shapiro ET, Strasser S, Nery J, Ricordi C, et al. Intraportal islet allografts in type-1 diabetes-mellitus – an update. *Diabetes Nutrition & Metabolis,* 1992;5(3):183-85.
- Alejandro R, Burke G, Shapiro ET, Strasser S, Nery J, Ricordi C, et al. Intraportal islet allografts in type 1 diabetes mellitus. *Transplant Proc* 1992:24(3):959-60.
- Alejandro R, Lehmann R, Ricordi C, Kenyon NS, Angelico MC, Gurke G, et al. Long-term function (6 years) of islet allografts in type 1 diabetes. *Diabetes* 1997;46(12):1983-89.
- Argibay P, Hyon S, Groppa R, Barbich m, Grossembacher L, Giudice C, et al. Initial experience with clinical islet transplantation in Argentina. *Transplant Proc* 1998;30(2):308.
- Bertuzzi F, Grohovaz F, Maffi P, Caumo A, Aldrighetti L, Nano R, et al. Successful [correction of Succesful] transplantation of human islets in recipients bearing a kidney graft. *Diabetologica* 2002;45(1):77-85.
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The following study was an old ECRI report and was not included in this report:

- ECRI. *Islet cell transplantation for type 1 diabetes mellitus.* ECRI, editor. Plymouth Meeting, PA: ECRI; 1999. 5.

The following study was an abstract without the information on the duration of diabetes for the participants and was not included in this report:

- Hering BJ, Kandaswamy R, Harmon JV, Ansite J, Clemmings S, Sakai T, et al. Insulin independence after single-donor islet transplantation in type 1 diabetes with hOKT3γ-1 (ala-ala), sirolimus, and tacrolimus therapy *Am J Transplant* 2001;1(Suppl 1).

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